UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/360,685	07/26/1999	ANTONELLO COVACCI	CHIR-0157	4520

27476 7590 02/28/2002

Chiron Corporation
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097

EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	PAPER NUMBER
1645	28

DATE MAILED: 02/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/360,685	Covacci et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 30, 2001*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *38-42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, 59-66, 68, and 70-* is/are pending in the application.

4a) Of the above, claim(s) *64 and 65* is/are withdrawn from consideration.

5) ☒ Claim(s) *72* is/are allowed.

6) ☒ Claim(s) *38-42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, 59-63, 66, 68, 70, 71,* and *73-80* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. *08/256,848*.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *23*
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Request for Continued Examination

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 08/01/01 (paper no. 19) has been entered.

Applicants' Amendment

2) Acknowledgment is made of Applicants' amendment filed 08/01/01 (paper no. 20). With these, Applicants have amended the specification.

Declaration under 37 C.F.R § 1.132

3) Acknowledgment is made of Applicants' submission of the Covacci Declaration filed 01/30/02 (paper no. 27) under 37 C.F.R § 1.132.

Information Disclosure Statement

4) Acknowledgment is made of Applicants' information disclosure statement filed 09/10/01 (paper no. 23). The information referred to therein has been considered and a signed copy of the same is attached to this Office Action (paper no. 28).

Election

5) Acknowledgment is made of Applicants' election, with traverse, of invention I, claims 38-42, 44, 45, 47, 48, 50-54, 56, 57, 59, 60-63, 66, 68 and 70-80, filed 11/30/01 (paper no. 26) in response to the restriction requirement mailed 10/22/01 (paper no. 24).

The Applicants' traversal is on the grounds that invention I and II are sufficiently related and that a search of the prior art relevant to all of the claims in the application would not cause substantial burden to the Examiner.

The Applicants' argument has been carefully considered, but is not persuasive. As clearly set forth in paragraph 4 of the restriction requirement mailed 10/22/01 (paper no. 24), inventions I and II are related as product and process of using the product of invention I. M.P.E.P 806.05(h)

permits the Office to separate the product from the process of using the product by showing that the product of one invention can be used in a materially different process. In the instant case, the polypeptide of invention I can be used as a diagnostic reagent in a materially different process, for example, a process of detecting antibodies in a sample to *Helicobacter pylori* CAI antigen. While the product belongs to class 530, the process of invention II is classified under a different class 424. Therefore, a search performed for the product would not be co-extensive to the process of invention II. For these reasons, the restriction requirement mailed 10/22/01 is maintained and is hereby made FINAL.

Status of Claims

6) Claims 67 and 69 have been canceled via the amendment filed 08/01/01.

New claims 71-80 have been added via the amendment filed 08/01/01.

Claims 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, 59-63 and 70 have been amended via the amendment filed 08/01/01.

Claims 64 and 65 have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

The elected claims 38-42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, 59-63, 66, 68 and 70-80 are under examination. An Action on the Merits for these claims is issued.

Priority

7) This application is a Divisional application of SN 08/471,491, filed 06/06/95, *now US patent 6,090,611*, which is a Divisional application of SN 08/256,848, filed 10/21/94, now abandoned, which is a national stage application of PCT/EP93/00472, filed 03/02/93 and PCT/EP93/00158, filed 01/25/93, which claim the priority benefit of the Italian application, SN FI 92A000052, filed 03/02/92.

Prior Citation of Title 35 Sections

8) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

9) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been

previously cited and made of record.

Objection(s) Maintained

10) The objection to the drawings made in the Office Action mailed 02/14/00 (paper no. 3) under 37 C.F.R.1.84 is maintained for reasons set forth therein. Applicants are asked to note the changes effected 03 May 2001, particularly the changes to the 'Timing of Corrections':

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85; 1097 O.G. 36

New formal drawings must be filed with the changes incorporated therein. The art unit number, application number (including series code) and number of drawing sheets should be written on the reverse side of the drawings. Applicant may delay filing of the new drawings until receipt of the "Notice of Allowability" (PTOL-37 or PTO-37). If delayed, the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability" to avoid extension of time fees. Extensions of time may be obtained under the provisions of 37 C.F.R 1.136(a) for filing the corrected drawings (but not for payment of the issue fee). The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the three month shortened statutory period set in the "Notice of Allowability" (PTO-37). Within that three month period, two weeks should be allowed for review of the new drawings by the Office. If a correction is determined to be unacceptable by the Office, Applicant must

arrange to have an acceptable correction re-submitted within the original three month period to avoid the necessity of obtaining an extension of time with extension fees. Therefore, applicant should file corrected drawings as soon as possible.

Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

Specification - Informalities

11) The specification is objected to for the following reasons:

(a) The amendment introduced to the first paragraph of the specification does not accurately reflect the current issued status of the earlier filed application(s) as indicated above in italicized letters under 'Priority'. Amendment to the first paragraph of the specification is needed to reflect this.

(b) The use of the trademarks in the instant specification has been noted in this application. For example, see page 39, last paragraph: "Tween 80 "; "Span 85" and "Squalene". Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification and make necessary changes wherever trademark recitations appear.

(c) On page 61, lines 4-6, the address of the American Type Culture Collection is incorrect. Effective 23 March 1998, ATCC has a new address: 10801 University Boulevard, Manassas, VA 20110-2209. Amendment to the specification is suggested to reflect this. It is suggested that Applicants examine the whole specification to make similar correction to the address, wherever it appears.

Rejection(s) Withdrawn

12) The rejection of claims 48, 50, 51, 53, 54, 56, 57, 59, 60-65 and 70 maintained in paragraph 9 of the Office Action mailed 10/24/00 (paper no. 15) under 35 U.S.C. § 112, first paragraph, as being non-enabled, is withdrawn. Applicants are asked to note the rejection made below.

13) The rejection of claims 38, 39, 42, 44, 45, 50, 54, 56, 66 and 68 maintained in paragraph

10 of the Office Action mailed 10/24/00 (paper no. 15) under 35 U.S.C. § 102(e) as being anticipated by Cover *et al.* (*Infect. Immun.* 58: 603-610, 1990), is withdrawn.

14) The rejection of claims 60 and 62 maintained in paragraph 12 of the Office Action mailed 10/24/00 (paper no. 15) under 35 U.S.C. § 103(a) as being unpatentable over Cover *et al.* (*Infect. Immun.* 58: 603-610, 1990), is withdrawn.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

15) Claims 40-42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, 59-63, 66, 68, 70 and 73-80 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 40, as drafted currently, does not distinctly claim the subject matter which Applicants regard as the invention, because the recitation "antigen comprising SEQ ID NO: 5" conveys that the claimed polypeptide antigen 'comprises' "SEQ ID NO: 5" which could be a nucleic acid sequence. The claim also lacks antecedent basis for the recitation "**the** *Helicobacter pylori* antigen", because there is no earlier recitation of "a" *Helicobacter pylori* antigen in the claim. Since the polypeptide comprising the amino acid sequence of SEQ ID NO: 5 is not "the" only antigen produced by *Helicobacter pylori*, it is suggested that Applicants amend the claim as shown below.

--40. A purified polypeptide of *Helicobacter pylori* comprising the amino acid sequence of SEQ ID NO: 5.--.

(b) Claims 60 and 62 are vague and confusing in the recitation: "a purified polypeptide of the *Helicobacter pylori* CAI antigen". Do Applicants mean to imply that there are more than one polypeptides of "the" *Helicobacter pylori* CAI antigen? The recitation used in these claims is inconsistent with the one used in claim 54, which includes the limitation: "the *Helicobacter pylori* CAI antigen".

(c) Claims 42, 45, 48, 51, 54, 61-63, 70, 73, 75 and 77-79 are vague and/or confusing in the recitation: "exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity", because it is unclear what function does not contribute, or does show substantially reduced contribution to what toxicity. Since the phrase does not appear to have been defined within the instant specification, it is not clear whether this toxicity

represents cytotoxicity, endotoxicity, exotoxicity, cell-vacuolizing toxicity, or any other type of toxicity.

(d) Claim 41, 44, 47, 50, 53, 56, 57, 59, 66, 68, 74, 76 and 80, which depend directly or indirectly, from one of the base claims rejected above, are also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, because of the indefiniteness or vagueness, identified above in the base claim.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

16) Claims 45, 54, 62, 68, 75 and 78 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Instant claims include the limitation: at least ten "contiguous" amino acids of SEQ ID NO: 5. However, there appears to be no descriptive support in the instant specification for a polypeptide that comprises at least ten "contiguous" amino acids of SEQ ID NO: 5. Applicants point to pages 14 and 16 of the specification as providing support for the limitation. However, no such descriptive support can be found in these parts of the specification for the term "contiguous". Therefore, the limitation in the claims is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to remove the new matter from the claim(s), or invited to point to the page and line number in the specification where support for such a recitation can be found.

17) Claims 45, 47, 48, 50, 51, 53, 54, 56, 57, 59, 61-63, 68, 70 and 73-80 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

Instant claims encompass a polypeptide comprising "at least 10" or "at least 15" amino acids, or contiguous amino acids of the *Helicobacter pylori* CAI antigen, a polypeptide of SEQ ID NO: 5, or of the second polypeptide, cytotoxin (CT) or heat shock protein (HSP), which polypeptide(s) can be used to induce the production of antibodies to *H. pylori* and which exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity. The limitation encompasses, for example, ten amino acid-long or fifteen amino acid-long fragments of recombinant or non-recombinant CAI antigen, and of the second *H. pylori* polypeptide, CT or HSP. However, the instant specification does not provide enablement for such polypeptide fragments having "at least 10" or "at least 15" contiguous or discontiguous amino acids of CAI antigen, a polypeptide of SEQ ID NO: 5, CT or HSP antigens of *H. pylori* having the recited characteristics. The precise structural composition of the claimed CAI, CT or HSP polypeptides comprising at least 10 or 15 amino acids is not disclosed such that one of ordinary skill in the art could produce such polypeptides which exhibit no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity and which can be used to induce the production of antibodies to *H. pylori*. There is a lack of disclosure as to which specific 10 or 15 contiguous or discontiguous amino acid residues of the CAI antigen, the polypeptide of SEQ ID NO: 5, CT or HSP are encompassed in the claimed polypeptide(s). It is uncertain whether retention of any 10 or 15 contiguous or discontiguous amino acid residues from any part of the CAI antigen, the polypeptide of SEQ ID NO: 5, CT or HSP (i.e., terminal or central parts) would yield polypeptides that would have the expected immunogenic functions and the capacity to exhibit no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity. Furthermore, there is no certainty that any 10 or any 15 amino acids in the recited polypeptides would retain *H. pylori*-specificity while conferring immunogenicity and non-toxicity

or substantially reduced toxicity to the polypeptides. The state of the art on bacterial polypeptides demonstrates the unpredictability associated with the presence of an epitope on any 10 amino acid-long fragment from any part of a given bacterial polypeptide antigen. Therefore, the immunogenicity of such a polypeptide antigen fragment, let alone its non-toxicity, is non-predictable. For example, McGuinnes *et al.* (WO 90/06696) clearly demonstrate that portions of an immunodominant bacterial polypeptide comprising ten contiguous amino acid residues from any random parts of the whole polypeptide molecule do not contain the antigenic epitope(s) that are recognized by the bactericidal (protective) antibodies (see entire document, especially Figure 5). Every 10-mer portions on this bacterial polypeptide did not contain such epitope(s) indicating that the prophylactic (protective) or therapeutic efficacy of any fragments from any portion of a bacterial polypeptide antigen is not a predictable event. Therefore, a 10-mer fragment from any portion of the instantly claimed *H. pylori* polypeptide(s) cannot be assumed to contain or retain the antigenic determinants that are needed for immunogenicity, or that induce prophylactic or therapeutic immune response. Clearly, the specification does not teach polypeptide fragments comprising 10 or fifteen amino acids of the CAI antigen, the polypeptide of SEQ ID NO. 5, CT or HSP which are non-toxic or substantially less toxic and at the same time, effective for use as a prophylactic or therapeutic vaccine against *H. pylori* infection. Without a disclosure of the specific amino acid residues contained within the claimed 10-mer or 15-mer polypeptide, one of ordinary skill in the art cannot be sure of the sequences embraced by the claims and would not be able to make and use those polypeptide sequences or fragments, as recited in the instant claims, for a prophylactic or therapeutic purpose, without undue experimentation.

The instant specification does not reasonably enable the recited polypeptide antigen(s) or its fragments that "exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity". The broadly recited toxicity encompasses cytotoxicity or cell vacuolizing/vacuolating activity. The specification on page 50, below the side heading "a. Immunodominance and cytotoxicity", teaches the vacuolizing cytotoxic activity of the non-recombinant CAI antigen samples on HeLa cells. The same is reflected in the state of the art. For instance, Oderda *et al.* (*Eur. J. Gastroenterol and Hepatology*, 5 (9): 695-699, 1993) teach the cytotoxin-associated p130 protein to be "strongly associated with cytotoxicity" (see page 695, left

column). Given that the specification is not enabled for a recombinant or non-recombinant CAI antigen or its fragments, having no toxicity or having substantially reduced 'toxicity', this description from the specification and/or the state of the art for the CAI is contrary to the limitation in the claims: "exhibits no ..... toxicity" or "substantially reduced functional toxicity". The vaccine, as claimed in some claims, also comprises a second polypeptide, such as, the toxic cytotoxin and a heat shock protein. The cytotoxin is known to have harmful cytotoxic activity, the CAI antigen is known to have cell vacuolating activity and therefore, both can additively cause severe pathologic effects rather than being able to treat or prevent a *H. pylori* infection.

The line bridging pages 38 and 29 describes that the instantly claimed vaccine may either be "prophylactic (to prevent infection) or therapeutic (to treat disease after infection)". Therefore, the claimed prophylactic vaccine should prevent *H. pylori* infection when administered before a subject acquires the infection, and the claimed therapeutic vaccine should have the capacity to treat *H. pylori* infection when administered after a subject acquires the infection. The instant specification on page 50, lines 15 and 16 indicates that the non-recombinant CAI polypeptide was used to immunize rabbits. However, ten amino acid- or fifteen amino acid-long fragments of the claimed CAI polypeptide, let alone the second polypeptide CT or HSP, are neither enabled as a prophylactic vaccine capable of preventing *H. pylori* infection, nor as a therapeutic vaccine capable of treating an already existing *H. pylori* infection. The instant specification lacks any animal or human data or evidence demonstrating the prophylactic or therapeutic efficacy of the claimed vaccine with or without the second polypeptide, or any serological evidence that is predictive of or correlative with prophylactic and therapeutic efficacy of the vaccine. Without an enabling disclosure and a concrete demonstration that the claimed polypeptide, especially any fragment comprising at least 10 or 15 amino acid residues, prevents a *H. pylori* infection, or treat an already existing *H. pylori* infection, with or without added homologous or heterologous antigens (CT or HSP), one of ordinary skill in the art cannot practice the invention as claimed. This is particularly important because the prophylactic or therapeutic efficacy of any 10-mer or 15-mer bacterial polypeptide antigen fragment is not a predictable event. Without a precise description and/or specific guidance, one of ordinary skill in the art cannot envisage which 10-mer or 15-mer parts on the recombinant or non-recombinant CAI polypeptide contribute to what

'toxicity'. Whether or not such products have functional or biologic capacity to be immunogenic, prophylactic and therapeutic is unknown and unpredictable, and would have required undue experimentation. The same holds true with respect to the second polypeptide, HSP or CT. Furthermore, the *Helicobacter pylori* HSP is known to and is described in the specification to be highly homologous with the HSP of all living organisms, including animals (see page 7 and 60). Induction of antibodies to such a molecule contained in a vaccine would potentially induce antibodies that can produce pathologic autoimmune consequences. A vaccine comprising such potentially autoimmune polypeptides cannot be viewed as a 'prophylactic' or a 'therapeutic' vaccine. Since which 10-mer or 15-mer fragment would retain *H. pylori* specificity and serve as a prophylactic or therapeutic vaccine against *H. pylori* infection while at the same time not produce harmful autoimmune antibodies against host tissues is neither disclosed, nor could be predicted and since the epitopes on the HSP responsible for therapeutic or prophylactic properties are not known or identified, one of ordinary skill would be forced into experimentation that is undue.

Therefore, given the lack of enabling disclosure and/or specific guidance, the lack of working examples, the state of the prior art with regard to the functional unpredictability and the structural composition of non-toxic and prophylactic or therapeutic fragments, the breadth of the claims and the quantity of experimentation necessary, undue experimentation would have been required by one of ordinary skill in the art to practice the invention. The claims are viewed as not meeting the enablement provisions of 35 U.S.C § 112, first paragraph.

Rejection(s) under 35 U.S.C § 102

18) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19) Claims 38, 42 and 44 are rejected under 35 U.S.C § 102 (b) as being anticipated by Hirschl *et al.* (*In*: *Helicobacter pylori, Gastritis and Peptic Ulcer*. (Ed) Malfortheiner *et al.* Springer-Verlag Berlin, pages 141-146, 1990).

The broad limitation "toxicity" is interpreted as encompassing toxicity due to endotoxin,

exotoxin, cytotoxin etc. It is also noted that the instant specification describes the term "purified" as follows:

> By "purified" ..... is meant, when referring to a polypeptide or nucleotide sequence, that the indicated molecule is present in the substantial **absence of other biological macromolecules of the same type**. The term "purified" as used herein preferably means at least 75% by weight, more preferably at least 85% by weight, more preferably at least 85% by weight, more preferably still at least 95% by weight, and most preferably at least 98% by weight, of **biological macromolecules of the same type present** (but water, buffers, and other small molecules, especially molecules having a molecular weight of less than 1000, can be present). [Emphasis added].

The above-cited description for the limitation "purified polypeptide" is interpreted as encompassing the claimed polypeptide that is partially purified, substantially purified or that which contains 75% to 98% by weight of biological macromolecules of the same type.

Hirschl *et al.* teach a highly purified *H. pylori* protein antigen with a molecular weight of approximately 120 kDa (see paragraph bridging pages 143 and 144 and Table 3). That Hirschl's highly purified 120 kDa polypeptide having a molecular weight as high as 120 kDa inherently contains an amino acid sequence comprising at least ten or fifteen amino acids and 'can be used to induce the production of antibodies to *Helicobacter pylori*' is inherent from the teachings of Hirschl *et al.* That Hirschl's highly purified polypeptide exhibits "a substantially reduced" functional contribution to toxicity is also inherently taught since it is well known in the art that highly purified polypeptides from a Gram negative bacterium exhibit substantially reduced endotoxicity.

Claims 38, 42 and 44 are anticipated by Hirschl *et al.*

20) Claims 38, 39, 42, 44, 48, 50, 60, 66, 71, 73, 74, 77 and 79 are rejected under 35 U.S.C § 102(b) as being anticipated by Clayton *et al.* (*In*: *Helicobacter pylori, Gastritis and Peptic Ulcer.* (Eds) Malfertheiner *et al.* Springer-Verlag, Berlin, pages 167-171, 1990).

It is noted that the instantly claimed protein is described on page 6 of the specification as having a molecular weight of "approximately 120-132 kDa". The term "vaccine" is defined on page 15 of the specification as a composition that is either 'immunogenic', **or** capable of eliciting partial or complete protection against *Helicobacter pylori*, a composition useful for treatment of an individual. It is also noted that the limitation "toxicity" encompasses toxicity due to endotoxin,

exotoxin, cytotoxin etc.

Clayton *et al.* teach a purified, immunodominant, recombinant 120 kDa polypeptide antigen of *Helicobacter pylori* (see 'Methods', 'Results' and 'Discussion' sections). Clayton *et al.* cloned the *H. pylori* 120 kDa polypeptide gene in *E. coli* (see page 167). Clayton *et al.* recombinantly expressed the *H. pylori* specific epitopes of the 120 kDa antigen (see page 171). The 120 kDa polypeptide was purified by SDS PAGE and electroelution (see page 168). That Clayton's purified recombinant polypeptide having a molecular weight as high as 120 kDa inherently contains an amino acid sequence comprising at least ten or fifteen amino acids and 'can be used to induce the production of antibodies to *Helicobacter pylori*' is inherent from the teachings of Clayton *et al.* Clayton *et al.* indeed used the purified polypeptide to raise antisera specific to the polypeptide in rabbits (see page 168). The process of raising antisera in rabbits using the purified recombinant polypeptide necessarily involves immunization of the rabbits with a vaccine containing an immunologically effective amount of the polypeptide antigen and a pharmaceutically acceptable carrier, and necessarily involves bringing into association the prior art polypeptide with a pharmaceutically acceptable carrier. That Clayton's polypeptide exhibits "a substantially reduced" functional contribution to toxicity is inherent from the teachings of Clayton *et al.*, since it is well known in the art that the purification process used in the prior art substantially removes from the polypeptide the general toxicity or the endotoxicity due to LPS.

Claims 38, 39, 42, 44, 48, 50, 60, 66, 71, 73, 74, 77 and 79 are anticipated by Clayton *et al.*

Rejection(s) under 35 U.S.C § 102/103

21) Claims 38, 39, 42, 44, 71, 73 and 74 are rejected under 35 U.S.C § 102(b) as being anticipated by, or in the alternative, under 35 U.S.C § 103(a) as being unpatentable over, Tummuru *et al.* (*In*: Abstracts of the 91st General Meeting of the American Society for Microbiology, Dallas, Texas, 5-9 May 1991, abstract B-127).

It is noted that the instantly claimed protein is described on page 6 of the specification as having a molecular weight of "approximately 120-132 kDa, preferably 128-130 kDa". It is also noted that the limitation "toxicity" encompasses general toxicity or toxicity due to endotoxin,

exotoxin, cytotoxin etc.

Tummuru *et al.* teach a potential immunogen and a unique 130 kDa antigen cloned from *H. pylori* after constructing a gene bank of total DNA of *H. pylori* in the lamda gt11 vector. The recombinant protein is not recognized by an antiserum to purified urease, but recognized by the sera from *H. pylori*-infected patients by immunoblot. The nucleotide and amino acid sequences of a digested genomic fragment showed an ORF that encodes the carboxy-terminal 130 amino acids of the deduced peptide (i.e., a polypeptide fragment) (see entire abstract). That Tummuru's recombinant protein or the 130-amino acid long fragment comprises at least ten or fifteen amino acids and that such a lengthy protein or its length fragment would inherently be immunogenic and have substantially reduced endotoxicity is inherent from the teachings of Tummuru *et al.* Therefore, Tummuru *et al.* anticipate the instant claims.

Alternatively, if one viewed Tummuru's cloned recombinant 130 kDa protein antigen or its 130-amino acid long fragment as an unpurified polypeptide, it would have been obvious to one of ordinary skill in the art at the time the invention was made to purify Tummuru's recombinant polypeptide or its fragment, using art known protein purification techniques to produce the instant invention, with a reasonable expectation of success. Since Tummuru *et al.* teach the recombinant 130 kDa protein antigen to be a potential immunogen that is recognized by sera from infected patients, one skilled in the art would have been motivated to further purify Tummuru's recombinant polypeptide or its fragment by using routine art-known protein purification techniques for the expected benefit of providing a much cleaner polypeptide immunogen, since purified polypeptides are ideally desired in the art for immunological characterization and studies related to serodiagnosis or evaluation of potential immunogenicity.

Claims 38, 39, 42, 44, 71, 73 and 74 are anticipated by, or in the alternative, as being *prima facie* obvious over, Tummuru *et al.*

Rejection(s) under 35 U.S.C § 103

22) Claims 60 and 77 are rejected under 35 U.S.C § 103(a) as being unpatentable over Clayton *et al.* (*In*: *Helicobacter pylori, Gastritis and Peptic Ulcer.* (Eds) Malfertheiner *et al.* Springer-Verlag, Berlin, pages 167-171, 1990).

It is noted that the specification at page 39 describes the "pharmaceutically acceptable

carriers" as including 'any carrier that does not itself induce the production antibodies harmful to the individual receiving the composition'. Exemplified pharmaceutically acceptable carriers include saline or glycerol, pH buffering substances, wetting or emulsifying agents or those that function as adjuvants (see page 40 of the specification).

The teachings of Clayton *et al.* have been explained above. If one viewed Clayton *et al.* as not teaching their purified recombinant polypeptide to be inherently containing a pharmaceutically acceptable carrier and therefore not teaching the method of bringing the polypeptide into association with such a carrier, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add or bring into association an art-known pharmaceutically acceptable carrier, such as, an alum or MPL adjuvant, with the Clayton's purified recombinant 120 kDa polypeptide of *H. pylori* to produce the product and the method of the instant invention, with a reasonable expectation of success. Adding to or bringing into association an art-known purified polypeptide antigen with an art-known pharmaceutically acceptable carrier would have been obvious to a skilled artisan, since it is a routine practice in the art to do so for the expected benefit of further enhancing the immunogenicity of the polypeptide antigen.

Claims 60, 62 and 77 are *prima facie* obvious over the prior art of record.

Relevant Prior Art

23) The prior art made of record and not currently relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Apel *et al.* (*Zentralbl. Bakteriol. Mikrobil. Hyg A* 268: 271-276, 1988, Applicants' IDS) teach a 120 kDa antigen band of *Campylobacter pylori* (i.e., *H. pylori*) which reacted by immunoblot with serum samples from patients with *Campylobacter pylori* infections (see abstract).

- Gerstenecker *et al.* (*Eur. J. Clin. Microbiol.* 11: 595-601, July 1992, Applicants' IDS) teach the **purified** 120 kDa protein antigen of *Helicobacter pylori* which reacted with specific antibodies in the sera of patients having *H. pylori* infections (see abstract).

- Crabtree *et al.* (*J. Clin. Pathol.* 45: 733-734, 1992, Applicants' IDS) teach the expression of a 120 kDa protein from *H. pylori* (see title). The protein was found by Western blotting to react with antibodies present in the antral biopsy culture supernatants from patients

with chronic gastritis (see abstract).

- Crabtree *et al.* (*Lancet* 338: 332-335, 10 August 1991) teach the immunoreactivity of gastric antibodies from dyspeptic patients with a 120 kDa protein of *H. pylori* by immunoblotting (see abstract).

- Hammermeister *et al.* (*Eur. J. Clin. Microbiol. Infect. Dis.* 11: 9-14, January 1992) teach the IgG and IgA antibody responses of German submarine crews to the 120 kDa protein of *H. pylori* (see abstract).

- Crabtree *et al.* (*Dig. Dis. Sci.* 36: 1266-1273, September 1991) teach the immune recognition by immunoblotting by the mucosal IgA of patients with *H. pylori* duodenitis *H. pylori* of the 120 kDa protein antigen of *H. pylori* (see abstract).

Remarks

24) Claims 38-42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, 59-63, 66, 68, 70, 71 and 73-80 stand rejected. Claim 72 is allowed.

25) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9306.

26) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

February 2002

S. DEVI, PH.D.
PRIMARY EXAMINER